REMARKS

I. Status of the claims

Claims 9-20 are pending. Claims 18-20 have been amended to more particularly define the immunosuppressant utilized in the composition. The claim amendments are supported by the specification and do not constitute new matter.[1]

II. Rejection of claims 9-20 under 35 U.S.C. § 112, second paragraph

Reconsideration is requested of the rejection of claims 18-20 under § 112, second paragraph as being indefinite.

The Office asserts that claims 18-20 are ambiguous because "cyclosporin" (used in claims 18 and 20) and "cyclosporin A" (used in claim 19) may refer to the same compound. Cyclosporin compounds encompass a class of fungal metabolites with potent immunosuppressive activity.[2] A number of different compounds belong to the cyclosporin family including cyclosporin A, cyclosporin G, and cyclosporin B.[3] Claims 18 and 20 have been amended by replacing "cyclosporin" with "a cyclosporin compound" so as to clarify that a cyclosporin compound is being claimed as opposed to a single compound within the cyclosporin family. Moreover, claim 19 has been

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[1]Claim 18 and 20 have been amended by adding "compound" after "cyclosporin." Support for this amendment is provided on page 3 of the specification. Claim 19 has been amended by replacing "cyclosporin A" with its chemical name. The specification has been similarly amended. The chemical name for cyclosporin A was well known in the art as of the filing date of the present application as evidenced by the STN search results provided by the Office along with paper 5 and thus, does not constitute new matter.

[2]See the specification at page 3 and Potier et al. (1998) 13:1406-1411, which discusses different immunosuppressive qualities of cyclosporin A and cyclosporin G and also discusses the cyclosporin family of compounds generally. A copy of Potier is enclosed with this Office action response and has been submitted with a supplemental IDS.

[3]See the specification at page 3.

amended by replacing "cyclosporin A" with its chemical name so as to more precisely define the cyclosporin compound being claimed.

In light of these amendments, claims 18-20 satisfy the requirements of §112, second paragraph.

III. Rejection of claims 9-20 under 35 U.S.C. § 102 (b) or (e)

Reconsideration is requested of the rejection of claims 9-20 under § 102(b) or (e) as anticipated by Isakson et al.[4] ("Isakson I"); Isakson et al.[5] ("Isakson II"), Isakson et al.[6] ("Isakson III), Gregory et al.[7]; Engelhardt et al.[8], Talley et al.[9], Hagmann et al.[10], Mills et al.[11], and Finke et al.[12].

A. The Cited Art does not Anticipate the Combination of Claims 9-20

Claim 9 is directed toward a composition comprising a **cyclooxygenase-2 inhibitor** (COX-2), a **5-lipoxygenase inhibitor** (5-LO) and an **immunosuppressive drug** selected from antiproliferative agents, antiinflammatroy-acting compounds and inhibitors of leukocyte activation.

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[4]U.S. Patent No. 6,136,839.

[5]U.S. Patent No.5,990,148.

[6]WO 96/41626.

[7]U.S. Patent No. 6,407,140.

[8]Chem. Abst. 125:292089.

[9]U.S. Patent No. 5,859,257.

[10]U.S. Patent No. 4,919,776.

[11]U.S. Patent No. 6,013,644.

[12]U.S. Patent No. 6,500,844.

Isakson I et al. and Isakson III et al. each disclose combinations and compositions comprising a COX-2 inhibitor and a 5-LO inhibitor. As noted by the Office, the cited art discloses that the pharmaceutical compositions may further comprise a pharmaceutically-acceptable carrier, diluent and/or adjuvant, "and, if desired, other active ingredients."[13] But nowhere do Isakson I et al. or Isakson III et al. disclose or suggest that the "other active ingredient" should be an **immunosuppressive drug**, as required by claim 9. selected from immunosuppressive agents

Gregory et al. disclose combinations comprising a COX-2 inhibitor, **a leukotriene A_4 hydrolase** (LTA4) inhibitor, and an immunosuppressive agent. Claim 9 requires a 5-L0 inhibitor not a LTA4 inhibitor. 5-LO inhibitors are not the same as LTA4 inhibitors.[14] Arachidonic acid may be oxygenated via either the cyclooxygenase pathway (to produce prostaglandins) or via the lipoxygenase pathway (to produce leukotrienes). 5-LO converts arachidonic acid to leukotriene A_4 (LTA4), which is then converted to LTB4 by the LTA4 hydrolase enzyme. Thus, an LTA4 inhibitor is different from a 5-LO inhibitor, in that the latter prevents the formation of LTA4 from arachidonic acid, while the former prevents the conversion of LTA4 to LTB4.

Isakson II et al. disclose combinations comprising a COX-2 inhibitor and **a leukotriene A_4 hydrolase** (LTA4) inhibitor. Isakson II et al. do not disclose a combination of COX-2 inhibitors, 5-LO inhibitors and an immunosuppressant, as required by claim 9.

Engelhardt et al. describe findings of a non-steroidal anti-inflammatory drug (NSAID), meloxicam. The abstract does disclose that meloxicam preferentially inhibits COX-2 leukocyte migration. But nowhere do Engelhardt et al. disclose the combination of COX-2 inhibitors, 5-LO inhibitors and an immunosuppressant, as required by claim 9.

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[13]See Isakson I, col. 31, line 46-51; Isakson II, page 46, line 27-33.

[14]See Isakson I, col. 1, lines 21-55.

Talley et al. disclose combinations comprising a COX-2 inhibitor and a 5-LO inhibitor. But they do not disclose a combination of COX-2 inhibitors, 5-LO inhibitors and an immunosuppressant, as required by claim 9.

Hagmann et al. disclose a class of substituted aminoquinolines that modulate chemokine receptor activity for use in the treatment of certain inflammatory and immunoregulatory disorders. Although Hagmann et al. disclose that their substituted aminoquinolines may be used in combination with **a** COX-2 inhibitor, **or a** 5-LO inhibitor, **or an** immunosuppressant, they do not disclose or suggest a combination having a COX-2 inhibitor along with a 5-LO inhibitor and an immunosuppressant, as required by claim 9.

Finke et al. disclose a class of substituted cyclopentyl compounds that modulate chemokine receptor activity that prevent the entry of HIV into a cell. Finke et al. do disclose that their substituted cyclopentyl compounds may be used in combination with **a** COX-2 inhibitor, **or a** 5-LO inhibitor, **or an** immunosuppressant. But nowhere do they disclose or suggest a combination having a COX-2 inhibitor along with a 5-LO inhibitor and an immunosuppressant, as required by claim 9.

Mills et al. disclose a class of spiro-substituted azacycles that modulate chemokine receptor activity for use in the treatment of certain inflammatory and immunoregulatory disorders. Although Mills et al. disclose that their substituted aminoquinolines may be used in combination with **a** COX-2 inhibitor, **or a** 5-LO inhibitor, **or an** immunosuppressant, they do not disclose or suggest a combination having a COX-2 inhibitor along with a 5-LO inhibitor and an immunosuppressant, as required by claim 9.

None of the art cited by the Office discloses a combination with the components of the claim 9 composition. A claim is anticipated only if each and every element as set forth in the claim is described in a single prior art reference.[15] Because the cited art

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[15]Verdegaal Bros. v. Union Oil Co. of Calif., 2 USPQ 2d 1051, 1053 (Fed. Cir. 1987). See MPEP §2131.

does not disclose every element of claim 9, the references do not anticipate claim 9. Moreover, claims 10-20, which depend from claim 9, are likewise patentable over these references for the reasons stated with respect to claim 9.

B. The Cited Art is not Available to Support a Rejection of Claims 9-20 under 35 U.S.C. § 102(e)

For the reasons detailed below, the art cited by the Office may not properly be used to support a 35 U.S.C. § 102(e) rejection of claims 9-20.

35 U.S.C § 102(e) specifically dictates that a person shall be entitled to a patent unless the invention was described in "a patent granted on an application for patent by another filed in the United States **before** the invention by the applicant for patent."[16]

The present application has an effective filing date of **February 13, 1996**: although filed on March 15, 2002, the present application is a divisional of application Serial No. 09/430,072 (now U.S. Patent No. 6,376,528), filed October 18, 1999, which was a continuation of application Serial No. 09/189,463 (now abandoned), filed November 10, 1998, which was a continuation of Serial No. 08/600,622 (now abandoned) filed February 13, 1996.

According to the face of the Hagmann et al. patent, the patent claims priority from provisional application Serial No. 60/033,536 ('536), filed December 20, 1996. Thus, Hagmann et al. is at most entitled to the filing date of the '536 application, i.e., December 20, 1996, more than eight months after the effective filing date of the present application.

The Finke et al. patent claims priority from provisional application Serial No. 60/139,067 ('067), filed June 11, 1999. Therefore, Finke et al. is at most entitled to the filing date of the '067 application, i.e., June 11, 1999, more than 3 years after the effective filing date of the current application.

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[16]35 U.S.C. §102(e)(2) (emphasis added).

According to the face of the Mills et al. patent, the patent claims priority from two provisional applications: provisional application Serial No. 60/032,890 ('890), filed December 13, 1996 and 60/033,535 ('535), filed December 20, 1996. Accordingly, Mills et al. at most is entitled to the filing date of the '890 application, i.e., December 13, 1996, more than eight months after the effective filing date of the present application.

According to the face of the Gregory et al. patent, the patent was a continuation of application Serial No. 08/600,655 (now abandoned), filed February 13, 1996. Therefore, Gregory et al. has a filing date of February 13, 1996, the **same day** as the effective filing date of the current application.

Because each of the Hagmann et al., Finke et al., Mills et al., and Gregory et al. patents have effective filing dates that are either before or on the same day as the effective filing date of the current application, they cannot properly be used to support a 35 U.S.C. § 102(e) of claims 9-20.

Isakson I et al. and Isakson II et al. were each filed June 11, 1996. Isakson I et al. is a continuation-in-part of application Serial No. 08/489,472 (now abandoned), which was filed June 12, 1995, and Isakson II et al. is a continuation-in-part of application Serial No. 08/489,468 (now U.S. Patent No. 5,700,816), which was filed June 12, 1995. In addition, the Talley et al. patent was filed August 14, 1996 and ultimately claims priority from an application that is a continuation-in-part of application Serial No. 387,680 (now abandoned), which was filed February 13, 1995. MPEP § 2136.03(IV) specifically states that the "filing date of a parent application [when the reference is a continuation-in-part of the parent] can only be used as the 35 U.S.C. § 102(e) date if it supports the claims of the issued child." No showing has been made by the Office that the respective parent application in each of Isakson I et al., Isakson II et al. or Talley et al. support the claims of the issued child (i.e. Isakson I et al., Isakson II et al., or Talley et al.) as required by MPEP § 2136.03(IV). Without this showing, Isakson I et al., Isakson II et al. and Talley et al. cannot properly be cited by the Office to support a 35 U.S.C. § 102(e) rejection of claims 9-20.

Isakson III et al. is a WIPO publication of an international application with an international filing date of June 11, 1996. Pursuant to MPEP § 2136.03(II), a WIPO publication of an international application filed prior to November 29, 2000, may not properly be used to support a 35 U.S.C. § 102(e) rejection.

Engelhardt et al. is a journal article published in 1996. In accordance with 35 U.S.C. § 102(e), journal articles, irrespective of their date of publication, may not be used to support a 35 U.S.C. § 102(e) rejection of claims 9-20.

In view of the above, applicants respectfully request a withdrawal of the rejection of claims 9-20 under 35 U.S.C. § 102(e).

Additionally, in its rejection, the Office asserts that the instant application is to be examined under 35 U.S.C.§ 102(e) as it existed prior to the amendment by the American Inventors Protection Act of 1999, because the application was not filed on or after November 29, 2000 or voluntarily published under § 122(b).[17] Applicants respectfully note that this statement is incorrect. 35 U.S.C. § 102(e) has been amended by the enactment of H.R. 2215, the Intellectual Property and High Technology Technical Amendments Act of 2002. In accordance with this amendment, MPEP § 2136 specifically dictates that revised 35 U.S.C. § 102(e), as amended by the AIPA, and as further amended by H.R. 2215, "applies in the examination of all applications, whenever filed."[18] The analysis provided above by applicants regarding whether the references cited by the Office may properly be cited in support of its § 102(e) rejection of claims 9-20 is consistent with the amendment of § 102(e) via H.R. 2215.

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[17]See Paper 5 at page 3.

[18]See the First Revision to the Eight Edition of the MPEP § 2136.

C. The Cited Art is not Available to Support a Rejection of Claims 9-20 under 35 U.S.C. § 102(b)

For the reasons detailed below, the art cited by the Office may not properly be used to support a 35 U.S.C. § 102(b) rejection of claims 9-20.

MPEP § 706.02(a) specifically dictates:

> If the publication or issue date of the reference [used in a 102(b) rejection] more than 1 year prior to the effective filing date of the application, the reference qualifies as prior art under 35 U.S.C. § 102(b).[19]

In this case, as detailed in III.B., the effective filing date of the present application is **February 13, 1996.** Consistent with MPEP § 706.02(a), to qualify as prior art against the present application under § 102(b), a reference must have an issue or publication date on or before **February 12, 1995**. According to the face of each of the Isakson I et al., Isakson II et al., Gregory et al., Hagmann et al., Finke et al., Mills et al., and Talley et al. patents the issue dates were October 24, 2000, November 23, 1999, June 18, 2002, July 6, 1999, December 31, 2002, January 11, 2000, and January 12, 1999, respectively. According to the face of Isakson III et al. , its international publication date was December 27, 1996. Moreover, the Engelhardt et al. journal article was published in 1996. None of the references cited by the Office were published or issued on or before February 12, 1995. The references, therefore, **are not** prior art under 35 U.S.C. § 102(b).

In view of the above, applicants respectfully request a withdrawal of the rejection of claims 9-20 under 35 U.S.C. § 102(b).

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[19]Also see 35 U.S.C. § 102(b).

IV. Rejection of claims 9-20 under 35 U.S.C. § 103(a)

Reconsideration is requested of the rejection of claims 9-20 under § 103(a) as obvious in view of Isakson I et al., Isakson II et al., Isakson III et al., Gregory et al., Engelhardt et al., Talley et al., Hagmann et al., Mills et al., and Finke et al.

A. The Cited Art is not Available to Support a Rejection of Claims 9-20 under 35 U.S.C. § 103(a)

In order to qualify as prior art to support a §103(a) rejection, each reference cited must qualify as prior art under 35 U.S.C. § 102.[20] According to the Office, Isakson I et al., Isakson II et al., Isakson III et al., Gregory et al., Engelhardt et al., Talley et al., Hagmann et al., Mills et al., and Finke et al. qualify as prior art under § 102(b) and/or (e). As detailed in III.B. and III.C, however, none of the references may properly be used to support a § 102(b) or (e) rejection of claims 9-20 and concomitantly, also may not be used to support a §103(a) rejection.

Moreover, effective November 29, 1999, 35 U.S.C. § 103(c) provides that subject matter which qualifies under 35 U.S.C.§ 102(e) **is not** to be considered when determining whether an invention sought to be patented is obvious under 35 U.S.C. § 103, provided the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person. Both the instant application and the Isakson I et al., Isakson II et al., Gregory et al., and Talley et al. patents have been assigned to G.D. Searle & Co.[21] In light of this common assignment, Isakson I et al., Isakson II et al., Gregory et al., and Talley et al. are unavailable to support a rejection of claims 1, 2, and 5-13 under 35 U.S.C. § 103.

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[20]See MPEP § 2144(II)(A)(1).

[21]Applicants can submit copies of the assignment documents for the each patent and the instant application upon request.

Accordingly, the rejection of claims 9-20 under 35 U.S.C. § 103(a) as obvious over Isakson I et al., Isakson II et al., Isakson III et al., Gregory et al., Engelhardt et al., Talley et al., Hagmann et al., Mills et al., and Finke et al. is improper.

B. The Cited Art does not Render the Combination of Claims 9-20 Obvious

The subject matter of a claim is *prima facie* obvious in view of particular references if the Office can demonstrate that (1) the references, alone or together, describe every element of the claims, (2) there is some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to combine the references, and (3) there is some reasonable expectation of success.[22]

As detailed in III A, the cited art taken singly does not disclose or suggest each element of the combination of claim 1. Moreover, as detailed in III A, the cited art taken collectively does not disclose or suggest a combination having the components of the claim 9 composition.

According to the Office, however, the art cited collectively "show that the combination of a COX-2 inhibitor, a 5-LO inhibitor and **other active ingredients** is well known in the art." This does not render claim 9 obvious. Claim 9 is not directed toward a composition comprising a COX-2 inhibitor, a 5-LO inhibitor and some "other active ingredient." Instead, it is directed toward a combination having a COX-2 inhibitor along with a 5-LO inhibitor and an immunosuppressant. For example, Isakson I et al. and Isakson III et al. disclose compositions comprising a COX-2 inhibitor, a 5-LO inhibitor "and, if desired, other active ingredients."[23] But the bare assertion found in Isakson I et al. and III et al. that the pharmaceutical compositions they describe may further

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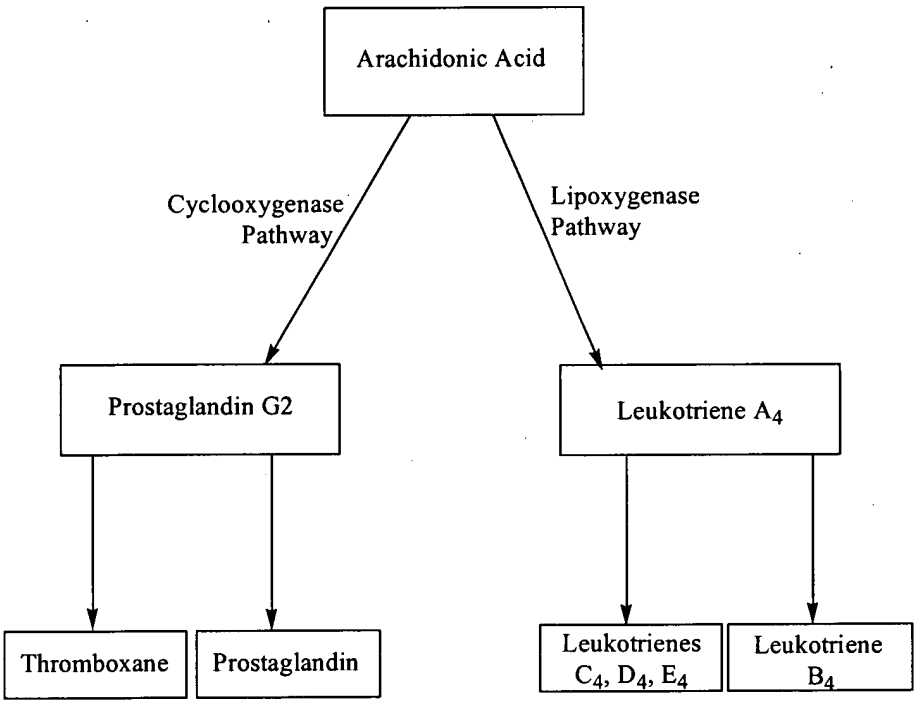
[22]See MPEP § 2142.

[23]See Isakson I, col. 31, line 46-51; Isakson II, page 46, line 27-33.

comprise, if desired, other active ingredients, would not have motivated one skilled in the art to select the particular immunosuppressive agents required by claim 9.

Moreover, considering the two separate biochemical pathways associated with the breakdown of arachidonic acid, it would not have been obvious to the skilled artisan to simply add an immunosuppressive agent to the composition disclosed by Isakson I et al. and III et al.(i.e. a COX-2 inhibitor and a 5-LO inhibitor) to arrive at the composition of claim 9. As detailed in the diagram below,[24] arachidonic acid may be oxygenated via either the cyclooxygenase pathway to produce prostaglandins or via the lipoxygenase pathway to produce leukotrienes.



Prostagladin G2 and leukotriene A4 are then converted into numerous other products, such as thromboxane, prostaglandins, or any of leukotrienes B4, C4, D4, or E4, which are direct mediators of numerous inflammatory responses. The composition

[24]See, for example, Kuby, Janis, Immunology, 3rd edition (W.H. Freeman and Company, 1997) at page 368. A copy of this page is enclosed.

disclosed in Isakson I et al. and III et al. effectively inhibits the breakdown of arachidonic acid via either the COX-2 mediated pathway or the 5-LO mediated pathway before any compounds that elicit an immune response are produced. A skilled artisan empowered with the disclosure of Iskakson I et al. and III et al. along with the knowledge of arachidonic acid metabolism, would not have added an immunosuppressant to the composition disclosed in Isakson et al. because the composition effectively prevents any immune response resulting from arachidonic acid metabolism, thereby seemingly making the need for an immunosuppressant unnecessary.

If anything, the collective disclosure of Gregory et al. and Isakson I et al. and III et al., actually teaches away from adding an immunosuppressive agent to the composition of claim 9. Referring to the diagram detailing arachidonic acid metabolism, the composition of Gregory et al. comprising a leukotriene A_4 hydrolase (LTA4) inhibitor, and an immunosuppressive agent inhibits the COX mediated pathway before any mediator of an inflammatory response is produced. But a LTA4 inhibitor only prevents the conversion of LTA4 to the proinflammatory agent, LTB4.[25] It does not prevent the conversion of LTA4 into the proinflammatory agents LTC4, LTD4 and LTE4. Gregory et al. include an immunosuppressive agent in their composition to diminish the immune response elicited by the proinflammatory factors LTC4, LTD4, and LTE4. The composition of Isakson I et al. and III et al., contrastingly, prevents any immune response resulting from arachidonic acid metabolism and they do not include an immunosuppressant in their composition. Taken together, the cited art teaches away from adding an immunosuppressant to a composition comprising a COX-2 inhibitor and a 5-LO inhibitor, as required by claim 9.

Unable to establish a *prima facie* case of obviousness, it appears that the Office has effectively slipped into an improper "obvious to try" analysis, informed by hindsight

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[25]See Isakson I, col. 1, lines 21-55; Isakson III, page1, line 16 through page 2, line 16.

which Applicants' disclosure affords. But the courts have consistently held that the test for a *prima facie* case of obviousness is not whether an invention is obvious to try.[26] Instead, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to combine the references, and there must be some reasonable expectation of success. The Office has not met this legal standard. Even assuming, *arguendo,* each reference cited by the Office discloses exactly what the Office says it does[27], the Office has provided no reason or rationale as to why a skilled artisan would be motivated to combine the disclosure of Isakson I et al., Isakson II et al., Isakson III et al., Gregory et al., Engelhardt et al., Talley et al., Hagmann et al., Mills et al., and Finke et al.. For example, why would it have been obvious to modify the composition disclosed in Isakson I et al. or III et al. so as to include an immunosuppressive drug as allegedly disclosed by Engelhardt et al.? Instead, the Office simply delineates bare assertions regarding what each reference purportedly discloses and then concludes that claims 9-20 are obvious. To properly establish a *prima facie* case of obviousness, the law requires more than conclusions supported by bare assertions.

For the foregoing reasons, the Office has failed to establish that claim 9 is *prima facie* obvious in view of the cited art. Moreover, claims 10-20, which depend from claim 9, are likewise patentable over these references for the reasons stated with respect to claim 9.

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[26]See In re O'Farrell, 7 U.S.P.Q.2d 1673, 1680-81 (Fed. Cir. 1988).

[27]See section III regarding Applicant's position on the correctness of the Office's interpretation of what the cited art discloses.

V. Conclusion

In light of the foregoing, Applicants request an entry of the claim amendments, withdrawal of claim rejections and solicit an allowance of the claims. The Examiner is invited to contact the undersigned attorney should any issue remain unsolved.

A check in the amount of $110.00 is enclosed for a one month extension of time. If there are any additional charges in this matter, please charge Deposit Account No. 19-1345.

Respectfully submitted,

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